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Guideline on clinical investigation of medicinal products in the treatment of Parkinson's disease

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Guideline on clinical investigation of medicinal products in the treatment of Parkinson's disease

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Executive summary

The present document should be considered as general guidance on the development for medicinal products for the treatment of Parkinson's disease and should be read in conjunction with other EMEA and ICH guidelines, which may apply to these conditions and patient populations.

Traditionally for Parkinson's disease different indications have been identified depending on the disease stage. Mostly these indications concerned symptomatic improvement in Parkinson's disease. The clinical development plan for these indications has been reasonably established. Confirmation of efficacy and safety is based on randomised double-blind, placebo-controlled and active-controlled parallel group studies.

Recent progress in basic science and molecular biology of the neurodegenerative diseases, including Parkinson's disease, has fostered interest in disease modifying agents. The number of trials evaluating products aiming to delay disease progression is increasing although no study design can be recommended definitely. For a disease-modifying claim a two-step procedure is foreseen, first a delay in disease progression should be shown, second an effect on the underlying pathological process should be established.

1. Introduction (background)

Parkinson's Disease (PD) is a common neurodegenerative disease neuropathologically characterised by the degeneration of heterogeneous populations of neural cells (mainly dopaminergic neurons) involving different neurotransmitter systems and different regions of the Nervous System. Degeneration process initiates in the olfactory nucleus and lower brainstem nuclei, and will extend to upper structures. The degeneration of the pigmented neurons in the pars compacta of the substantia nigra accounts for most of the distinctive motor symptoms. The presence of eosinophilic cytoplasmatic inclusions (Lewy bodies) in the remaining cells of pigmented nuclei and other brain regions is essential for the neuropathological diagnosis. The Lewy bodies are however, not unique for PD. The Lewy bodies are found in Alzheimer’s Disease and in the elderly.

The incidence of PD is estimated at 4.5-16/100.000 persons/year. PD is rare before 50 years of age. Incidence rates increase with age from 5/100.000 in the 45-49-age group up to 90/100.000 in the over 75-age group. Prevalence estimates range from 18-328/100.000. The overall prevalence of PD for subjects aged 65 years or older is 1.6%. Prevalence increases with age, from 0.6% in the 65-69-age group up to 3.5% in the 85-89-age group.

The clinical diagnosis of PD requires bradykinesia and at least one of the following: resting tremor, muscular rigidity and postural reflex impairment (core symptoms). Diagnosis of PD requires the exclusion of other causes of Parkinsonism and Parkinsonian syndromes e.g. progressive supranuclear palsy, multiple system atrophy, drug induced Parkinsonism and post-encephalitic Parkinsonism. Misclassifications, especially in early-stage PD, occur frequently. However, around 75% of the diagnosis of PD is correct if 2 out of the 4 core symptoms are present and other neurological sign/symptoms absent. In addition, Magnetic Resonance Imaging may be helpful for excluding other Parkinsonian syndromes. In 15%-25% of the clinical diagnosis, PD cannot be confirmed histopathologically. The role of biomarkers for the diagnosis of PD is uncertain.

Other signs and symptoms that may be present or develop during the progression of the disease are autonomic disturbances (sialorrhoea, seborrhoea, constipation, micturition disturbances, sexual

functioning, orthostatic hypotension, hyperhydrosis), sleep disturbances and disturbances in the sense of smell or sense of temperature.

Depressive symptoms and cognitive dysfunction develop in up to 45% and 35% of Parkinson's patients respectively. There are no distinct clinical features that distinguishes depressive symptom in PD from depression. With respect to cognitive function there is a considerable overlap in clinical and neuropathological features with other dementing disorders. Parkinson's Disease Dementia (PDD) is strictly related to Dementia with Lewy Bodies (DLB) but may overlap considerably with Alzheimer's Disease. Most neuropathological studies in patients with PDD report the co-existence of a substantial amount of Alzheimer's amyloid plaques. Clinically cognitive dysfunctions in PDD and Alzheimer may converge as the disease progresses although at in the early stages the spectrum of cognitive deficits may be different. Whether Dementia with Lewy Bodies and PDD are different entities is not settled.

PD is slowly progressive. Severe disability or death may be expected in 25% of the patients within 5 years, in 65% of the patients within 10 years and in 80% of the patients within 15 years of onset.

Ideally treatment should stop further neurodegeneration and delay disease progression. However the mechanisms responsible for the dopaminergic cell loss in PD is unknown. No pharmacotherapy currently exists that has shown a relevant delay in disease progression.

Current pharmacological intervention in PD is symptomatic. Improvement of the impaired dopaminergic neurotransmission is the backbone of pharmacotherapy. Patients with early stages of PD may start, depending on the clinical context, with a dopamine-agonist or a dopamine precursor (L-Dopa+)[1].

In general, a patient with early stages PD will start with dopamine-agonists. If symptoms are insufficiently controlled L-Dopa+ is added during the course of the disease. In advanced PD most patients will receive both L-Dopa+ and a dopamine-agonist.

Motor complications will develop during the course of the disease. Frequently they are referred to as L-Dopa+ induced motor-complications. However, the mechanisms leading to these motor complications are not fully understood. Most likely the effect of L-Dopa+ is modified as a consequence of the loss of dopaminergic cells as there is no evidence that L-Dopa+ itself has a deleterious effect on disease progression.

L-Dopa+ dose-limiting factors are the occurrence of involuntary movements (dyskinesias, dystonia, chorea-athetosis) psychiatric side effects (e.g. hallucinations, delusions, psychosis) and autonomic side effects (e.g. orthostatic hypotension). Dopamine-agonists act directly on the dopamine receptors. However, compared to L-Dopa+, dopamine-agonists are relatively less effective and have a higher incidence of psychiatric and autonomic side effects.

Other drug categories such as monoamine oxidase inhibitors, catecholamine-O-methyl transferase inhibitors, anticholinergics and glutamate modulators may represent an alternative, or more often an adjunctive treatment to L-Dopa+ and dopamine-agonists.

Non-pharmacological interventions include deep brain structures stimulation and neuronal grafts. Deep brain structures stimulation is limited to highly selected patient groups. Neuronal grafts mainly have an investigational status.

[1] With L-Dopa+ the combination levo-dopa and a peripheral dopa-decarboxylase inhibitor is indicated

2. Scope

The scope of this document is restricted to PD with some remarks concerning PDD and depression in PD.

3. Legal basis

These notes are intended to provide guidance for the evaluation of drugs in the treatment of Parkinson's disease. They should be read in conjunction with the Directive 2001/83/EC, as amended and current and future EC and ICH guidelines, especially those on:

- Studies in support of special populations: geriatrics (ICH E7);
- The extent of population exposure to assess clinical safety for drugs intended for long-term treatment in non life threatening conditions (ICH E1);
- General considerations for clinical trials (ICH-E8);
- Guideline on Clinical Trials in Small Populations;
- Statistical principles for clinical trials (ICH-E9);
- Choice of Control Group in Clinical Trials (ICH E10);
- Note for Guidance on the Investigation of Drug Interactions;
- Pharmacokinetic studies in man;
- Clinical testing of prolonged action forms, with special reference to extended release forms;
- Dose response information to support product authorisation (ICH E4);
- Guideline on medicinal products for the treatment of Alzheimer's disease and other dementias (CPMP/EWP/553/95, Rev. 1).

They are intended to assist applicants in the interpretation with respect to specific problems presented by products in PD.

4. Specific considerations

In developing medicinal products in the treatment of PD specific problems can be found. These problems are discussed in this section.

4.1. Design of the clinical studies

Clinical studies in PD are hampered by the long duration and slow progressive course of the disease, the variability and heterogeneity of symptoms and signs, cyclic episodes in severity of the symptoms/signs over the day related to the time of medication and polytherapy. In addition, misdiagnosis, co-morbidity and co-medication add to the heterogeneity of the patient population.

The design of the clinical trials in PD depends on the objectives of the study. The following study objectives may be distinguished:

- Symptomatic relief in early-stage PD before L-Dopa+ treatment;
- Symptomatic relief in patients with PD on L-Dopa+ subdivided in:

- Patients on L-Dopa+ with insufficient control of motor symptoms;
- Patients on L-Dopa+ with motor fluctuations;
- Patients with serious unpredictable and rapid changing motor fluctuations.

- Therapies aimed to modify disease progression, late motor complications;
- Treatment aimed to postpone late motor fluctuations;
- Treatment aimed to delay disease progression;
- Substitution of neuronal loss.

It is acknowledged that some of the objectives may overlap in PD population. Therefore these objectives are a guide and there may be other objectives that can be justified.

In addition some remarks concerning studies in PDD and PD associated depression are made.

Symptomatic relief in early-stage Parkinson's Disease before L-Dopa+ treatment

Double-blind placebo-controlled studies of at least 6-month duration (excluding the titration period, where dose adaptations of the test drug are allowed), are recommended to establish efficacy, maintenance of efficacy and safety.

Main efficacy variable should focus on the improvement of the core symptoms, i.e. motor symptoms.

In *de novo* patients[2], the clinical development plan should include three-arm randomised double-blind placebo-controlled studies. Motor symptoms in general are highly variable and fluctuating motor symptoms in PD are not an exception in this respect. This is even more prominent in early-stage PD where symptoms are mild. Thus incorporation of a placebo-arm allows the distinction between a genuine treatment effect and spontaneous variations in motor symptoms in early-stage PD. The positive control arm aims to demonstrate a similar or better benefit/risk balance of the test drug as compared to an acknowledged standard product in early-stage PD. The choice of the comparator and the dose used should be justified. For patients that may have received dopaminergic treatment for a short period a washout period will be needed.

Symptomatic relief in patients with Parkinson's Disease on L-Dopa+

In patients with some form of advanced PD the test drug may be given as adjunctive to L-Dopa+. These patients may suffer from an insufficient control of motor symptoms despite treatment with L-Dopa+ or may suffer from dose dependent or non-dose dependent motor fluctuations.

Patients on L-Dopa+ with insufficient control of motor symptoms

In patients on L-Dopa+ with insufficient control of motor symptoms the existing L-Dopa+ therapy should be optimised before the test-drug/placebo is added. After the test drug is added L-Dopa+ dose should be kept stable. Otherwise it will not be possible to distinguish between an effect of the test drug and an increased efficacy due to the optimised L-Dopa+ dose regime. Three-arm placebo- and active-controlled trials of three month duration are recommended.

Endpoint should be the improvement of the core symptoms, i.e. motor symptoms and activities of daily living (see section 5.1 Methods to assess efficacy).

Patients on L-Dopa+ with motor fluctuations

[2] Here defined as patients with recently diagnosed Parkinson's Disease (3-6 months) and no previous dopaminergic treatment except for a short period (< 30 days).

It is common practice to make a distinction between dose and non-dose dependent motor fluctuations, to speak of late motor complications, L-Dopa+ induced late motor complications and motor fluctuations in the 'end stage' PD. Paroxysmal on-off phenomenon, freezing, dyskinesia in on-phase are usually considered less related to the time of dosing, and hence less predictable.

These distinctions are somewhat arbitrary as they are neither separate entities (e.g. same type of motor fluctuation may occur in all categories) nor mutually exclusive. They are however of pragmatic value as they indicate possible treatment options (e.g. change in dosage regime). The text below should be read keeping this in mind.

Predictable motor fluctuations are related to the time of dosing e.g. peak dose dyskinesias, end of dose deterioration, wearing off and biphasic dyskinesias. Delayed-on is a prolongation of the time required for an anti-Parkinsonian drug effect to appear.

An effect on predictable motor fluctuations should be proven by comparing the effect of the new treatment regime to the standard treatment regime. The term treatment regime is used here to capture different formulations as well as different devices with the same agents. As an example a slow release L-Dopa+ should be compared to an immediate release L-Dopa+ formulation. A benefit of the new treatment regime as compared to the standard treatment regime should be established. Study duration of 3 months is recommended. Likewise there are arguments that continuous stimulation instead of a pulsatile stimulation of the dopamine-receptors lead to less, or even, delay late stage motor complications irrespective whether they are dose/non-dose dependent. Such claim would require confirmation in comparative superiority studies.

For less predictable motor fluctuations (e.g. paroxysmal on-off phenomenon, freezing) therapy intends to reduce the duration and/or intensity of "OFF"-periods. Hence, main efficacy variable should be the decrease in number, duration and/or intensity of "OFF"-periods. It should also be clear to what extent "ON"-time <u>with</u> dyskinesia and "ON"-time <u>without</u> dyskinesia is increased. Derivation of a responder variable, for instance a patient with an x amount of reductions and x quantity increase in on/off time might be helpful.

In addition the relative efficacy and safety compared to the standard product for symptomatic relief in advanced PD should be known. Therefore the clinical development plan should include three arm randomised double-blind placebo-controlled studies wherein a test drug arm, a standard drug arm and a placebo arm, all in addition to L-Dopa+. Study duration should be of at least 3 months excluding the titration phase.

In all conditions concomitant L-Dopa+ and other relevant medication should be kept constant during the trial. A reduction in L-Dopa+ dosage is not appropriate as primary efficacy variable, but should be recorded for validation of the study design to provide reassurance that treatment effects are not due to dose reductions in L-Dopa+. However, Parkinson patients may suffer from both dose dependent and non-dose dependent motor fluctuations simultaneously. In such cases it might not be possible to keep the relevant concomitant medication constant. However, efficacy on non-dose dependent motor fluctuations can only be claimed if such effect does not negatively affect dose-dependent motor fluctuations or "OFF"-time.

Patients with serious, unpredictable and rapid changing motor fluctuations

In highly advanced PD, patients may suffer from severe and highly unpredictable motor fluctuations that may succeed each other rapidly during the day.

Continuous delivery devices of L-Dopa+ or dopamine-agonist subcutaneously, intravenously or by a duodenal catheter have been shown to be beneficial.

For proving efficacy randomised blinded comparative studies are needed showing a reduction of the motor fluctuations. Superiority should be shown against placebo in the add-on setting or against a treatment regime with the conventional route of administration. Alternative study designs (e.g. n of 1 trials) may be considered. Referred to is the Guideline on Clinical Trials in Small Populations.

For safety number of subjects and follow-up time should be sufficient to make a safety assessment. No detailed recommendations can be made as this also depends on the substance and device used.

Therapies aimed to modify disease progression: Postponement of late motor complications

When the drug studied is aimed at postponing late motor complications the trials should be long term double-blind, placebo-controlled add-on studies wherein the test drug or placebo is added to L-Dopa+. Duration of the study should be sufficient to show an effect. Given the expected time window wherein late motor complications develop the study may last for years. Primary efficacy variable should be time to late motor complications as pre-specified in the protocol. The reduction in L-Dopa+ doses as primary efficacy variable is not recommended. However, it is necessary to take into account L-Dopa+ reductions when evaluating other efficacy variables in the light of these reductions.

New study designs concerning postponing late motor complications may be developed but should be justified.

Therapies aimed to modify disease progression: Treatment aimed to delay disease progression

The number of trials evaluating products aiming to delay disease progression is increasing. Ideally a disease modifying effect should be separable from a symptomatic effect. There is however, no universal study design that can be recommended.

As general principle studies should be randomised, placebo-controlled and long-term. In general, the time to that milestone event or proportion of subjects reaching that milestone may be the primary endpoint. The event of interest and duration of study depends on the Parkinson population studied:

- Early untreated PD (*de novo* patients): The goal is to slow the progression of motor symptoms by assessing change in UPDRS, or time to L-Dopa+/DA-agonists. The proposed trial duration should be sufficiently long, probably up to 24 months.

The change in UPDRS may be evaluated by a slope analysis. Extrapolation of the slope beyond the observation period requires a linear progression rate. This assumption needs to be justified and might be different depending on the population included and duration of observation. Hence the clinical relevance of difference in slope may be difficult to assess. Moreover the progression rate in the placebo group is dependent on the population selected. Given these reservations with respect to the slope analysis, alternative analysis, if justified, may be more appropriate.

Further caveats concern the use of time to L-Dopa+ which requires highly standardised assessments.

- Stable treated PD: the goal is to slow further decline of motor impairment, progression of disability, prevent motor complications and prevent non-motor complications. Studies may demand 2-5 years. Key outcomes measurements for this stage could be the emergence of so-called axial symptoms: e.g. freezing of gait, loss of balance or Hoehn & Yahr stage III.

- In advanced PD the prevention of disability becomes the key therapeutic goal. Clinical endpoints are also wide-ranging including; autonomic failure, falls, cognitive symptoms and possibly 'time to' dementia and 'time to' nursing home placement. Clinical studies for this population could extend over five years.

Biomarkers measuring the cerebral dopamine uptake (SPECT-β-CIT) or dopamine-receptor density (PET-F-dopa) cannot be considered sufficient surrogate biomarkers. Although these are biomarkers for nigrostriatal function it is not established that they correlate to a meaningful, measurable and persistent changes in clinical function. Simultaneous assessment of clinical outcome and biomarkers is recommended in order to evaluate whether both are causally associated and to assess the potential predictive value of a biomarker for clinical outcome. Of note current imaging techniques are not predictive for non-dopaminergic related symptoms.

If a delay in disease progression is shown, this does not imply that a new agent is also a disease modifier. This requires the demonstration of an effect on the underlying pathophysiology of the disease by e.g. biochemical markers or neuroimaging measures.

Therefore for a disease-modifying claim a two-step procedure is foreseen, first a delay in clinical measures of disease progression should be shown, second an effect on the underlying pathophysiology process which correlates to a meaningful, and persistent changes in clinical function.

Substitution of neuronal loss

Cell therapy in the CNS is confined to the experimental stage. In PD there are a lot of uncertainties that remain to be settled e.g. the source of tissue, the selection of patients, number of cells required, need for immunosuppressant and/or growth factors, most successful surgical procedures, need and feasibility of sham surgery and so on.

Although no detailed recommendations can be given it should be demonstrated that the grafted neurons survive and are functional. Therefore survival of the graft as shown by for instance PET imaging has to be supported by long term improvements of motor function.

Treatment of cognitive dysfunction in Parkinson's Disease

PDD and Dementia with Lewy Bodies (DLB) are subsumed under the umbrella Lewy Body dementia. Based on the clinical features and temporal sequence of the key symptoms the diagnosis is PDD or DLB. In the early stages, PDD cognitive deficits are characterised by impairment in executive function, attention and working memory that is substantiated by the presence of major Parkinsonian motor symptoms. In contrast the major feature of Alzheimer's disease is a progressive memory loss from the beginning.

Operationalised criteria for patients with PDD have been proposed recently, however data on sensitivity and specificity have not been established. A current pragmatic approach requires at least one year of major Parkinsonian motor symptoms before the onset of symptoms of dementia.

The criteria by McKeith et al. have become a standard for studies in dementia with Lewy Bodies (DLB), which show a very high specificity but low sensitivity. Clinical core features of DLB consist of rapid fluctuations in cognition, recurrent visual hallucinations and spontaneous and fluctuating features of parkinsonism. These are further supported by high sensitivity for extrapyramidal side effects to neuroleptics and rapid eye movement sleep behaviour disorder. For a specific claim of efficacy in PDD, efficacy should be shown on cognition and ADL. Referred to is the guidance on Alzheimer's disease.

Treatment of depressive symptoms in Parkinson's Disease

As it is still under discussion whether depression in PD can be separated from major depressive episodes no recommendation can be made. As a consequence a specific indication as treatment of depression in PD as a separate entity cannot be made at this time.

4.2. Dosage

It is customary to titrate a new anti-Parkinson drug until an optimal effect is seen or until the maximal tolerated dose is reached or up to the maximal doses allowed, whatever comes first, where after patients enter the maintenance period. In the maintenance period, patients should stay at their individual determined optimal dose level. Therefore the criteria of an optimal effect and intolerance should be unambiguously and carefully defined in the study protocol. It is not recommended to leave the definition of the optimal response to the individual investigator. Also the criteria for starting the maintenance period should be carefully defined.

Titration of doses for individual patients according to response as defined by the individual investigator may lead to dose recommendations which are broad and vaguely described. The clinical development plan should contain well-designed dose-finding studies in order to justify the dosage used in confirmatory clinical trials and dose recommendation in the SPC. These dose-finding studies should incorporate randomised arms in which patients are titrated to fixed doses which are maintained for the subsequent maintenance period. A flexible dose arm could also be included for comparison.

4.3. Polytherapy

Parkinsonian patients usually use more than one anti-Parkinson drug and dose adaptations during the course of the disease or the clinical trial are usual. The effect of the test drug in PD should be clearly distinguished from effect due to simultaneous adaptations in doses of concomitant anti-Parkinson drugs given. This might be done by keeping these drugs unchanged for the duration of the clinical trial or by using a placebo-arm in comparative studies. Concomitant anti-Parkinson drug use should be stable for at least 4 weeks prior study entry. Moreover, one should keep in mind that some anti-Parkinson drugs (e.g. MAO-B-inhibitors) preserve their activity for a long time after the drug is stopped. If such drug is stopped before the start of the trial the washout period should be sufficient.

Due to additive adverse events however, it might be impossible to keep the concomitant medication unchanged during the trial.

For studies wherein patients received polytherapy the study protocol should contain a detailed section how to deal with patients receiving concomitant concurrent agents. Moreover, the analysis plan should address how the effect size of the test agent can be separated from the effect due to changes in concomitant therapy in those patients where the concomitant anti-Parkinson therapy has been changed.

5. Assessment of efficacy criteria

5.1. General remarks

The primary efficacy variables should stick as close as possible to the aim of the study, as described in point 4.1.

Moreover, efficacy should be expressed in clinically interpretable terms. Therefore it is recommended to evaluate efficacy in terms of success and failure (e.g. degree of symptom reduction from baseline experienced by responders). A responder should be defined by the applicant and the clinical relevance of this definition justified. Success and failure may also be defined in terms of time to event depending of the study aim (see section 4.1).

Estimates of treatment effects with 95% confidence intervals should be discussed in relation to their clinical relevance.

A priori the choice of endpoints and clinical relevance of expected effects (e.g. difference in proportion of responders) have to be discussed in the protocol with reference to other comparative data or relevant publications.

Secondary efficacy variables such as timed performance tasks provide supplemental evidence of efficacy.

5.2. Methods to assess efficacy

The validity, sensitivity, reliability of the rating scales used should be justified. Intra-rater and inter-rater reliability should be known or assessed.

For example, for the assessment of motor function in PD the UPDRS II (activity of daily life) and UPDRS III (motor-examination) are accepted and validated scales. Moreover, their use will facilitate the comparison between studies. However, the UPDRS II and UPDRS III have their own dis- and advantages. Especially in assessing dyskinesias the UPDRS IV is not appropriate and the UPDRS II is not acceptable without additional scoring of dyskinesias. It should be kept in mind that scales alternative to the UPDRS, if validated and justified, may be more appropriate depending on the specific medical condition studied.

When "OFF"-time or "ON"-time, is the main efficacy variable an operational definition of what will be considered an "OFF" and "ON" period should be established. It should be also clear to what extent "ON"-time <u>with</u> dyskinesia and "ON"-time <u>without</u> dyskinesia is increased. Patients changing from "OFF" to "ON" <u>with</u> dyskinesia should be asked whether they consider this an improvement or not.

In scoring motor functioning standardised timing of efficacy assessments is essential given the cyclic episodes in severity of the symptoms/signs over the day related to the time of medication and circadian rhythms. Moreover, symptom scores over time should be assessed, for "ON"-periods and "OFF-periods" separately, if applicable.

For both, assessment of motor function and/or "ON"-, "OFF"-time with/without dyskinesias, the evaluation by the patient by means of a diary is needed. Patient's diaries scoring the type of dyskinesias (disabling/non-disabling) over predefined periods on pre-specified days during the trial are recommended.

The use of indirect efficacy variables as primary efficacy variable in pivotal studies, such as an improvement in the clinical global impression, quality of life, or L-Dopa+ savings is not recommended unless the association between these variables and improvement in core symptoms or motor fluctuations or handicap has been proven.

6. Selection of patients

6.1. Study population

The diagnostic criteria used should be mentioned in the protocol and justified by the company. The inclusion and exclusion criteria should be such that the population is clearly defined and be in accordance with the study objectives.

These criteria must exclude patients with a high suspicion of other parkinsonian syndromes. Especially in early PD there may be diagnostic uncertainty about whether a patient suffers from PD or from a parkinsonian syndrome. In some cases the L-Dopa+ test may be helpful at least in discriminating between responders and non responder on L-Dopa+. Only those patients with a clear-cut response to L-Dopa+ should enter a trial although there is still a risk of including a patient with a parkinsonian

syndrome instead of PD. It is recommended that the number of patients recruited be increased to allow for misclassifications which occur frequently, especially in early-stage PD.

For staging the severity of PD the Hoehn & Yahr scale may be used but other scales might be appropriate as well.

Depending on the aim of the study, the inclusion criteria for severity of the disease, severity of functional impairment/handicap, severity of motor fluctuations, should be carefully defined.

Stratification according the use of concomitant anti-Parkinson drugs at randomisation, if, applicable, is advised.

7. Strategy/Design

7.1. Pharmacodynamics

There are no specific human pharmacodynamic models for studying anti-Parkinson drugs. Consequently, the evidence which can be provided from pharmacodynamic studies is unclear.

The apomorphine test and L-Dopa+ test as a pharmacodynamic model for measurement of the responsiveness to single doses of the investigational drug in patients with an advanced PD are considered too insensitive.

As pharmacological effects on cognition and/or memory and/or psychological function and/or reaction time are expected, these should be studied.

7.2. Pharmacokinetics

The pharmacokinetics of the drug should be thoroughly described, in that the absorption, bioavailability and route(s) of elimination (including metabolites and enzymes involved) should be characterised. Referred to are the specific PK guidances.

7.3. Interactions

Pharmacokinetic interactions between the test drug and anti-Parkinson drugs, expected to be given simultaneously with the test drug in clinical practice, should be studied, unless clear mechanistic based evidence is available that no interaction could be expected. Referred to is the interaction guideline. All pharmacodynamic interactions between the test drug and any anti-Parkinson drug, expected to be given simultaneously with the test drug in clinical practice, should be studied. Also potential pharmacodynamic interaction with alcohol and CNS active drugs should be investigated. If relevant, pharmacokinetic studies of the study drug in patients with hepatic and /or renal impairment should be performed.

7.4. Therapeutic studies

Initial therapeutic studies

The purpose of this phase of investigation is to obtain initial information on safety, to establish preliminary evidence of activity, suitable therapeutic dose ranges and frequency of dosing. Dose ranging studies should be performed in a controlled, titration and/or fixed dose design, using at least 3 dosages, to establish the lower end of the clinically effective dose range as well as the optimal dose. Determination of plasma levels may be useful.

Main therapeutic studies

The main study designs have been discussed under the heading specific considerations (point 4.).

The three arms studies recommended should be large enough to allow comparison of the efficacy of active comparators i.e. the applicant should justify the level of precision.

Prior and concomitant anti-Parkinson medication has to be documented in detail. Medication interfering with the study drug should be washed out. Adaptations in concomitant anti-Parkinsonian medication during the study also have to be documented in detail.

7.5. Statistical analysis

Reference is made to the ICH-E9 statistical principles for clinical trials.

In PD, the analysis of efficacy should evaluate the effect in the maintenance period where patients are stabilised on a fixed dose of the study drug.

In studies of symptomatic relief in newly diagnosed Parkinson 's disease patients, patients may have received dopaminergic treatment for a short time period. A separate analysis for patients naïve/not naïve to dopaminergic treatment in these studies is expected in order to evaluate possible carry over of pharmaco-dynamic effects.

The primary analysis should take into account stratification factors used for randomisation as usual and the use of concomitant anti-Parkinson drugs at baseline. Results should be interpreted in the light of changes in concurrent co-medication during the trial (see section 4.1 Design of clinical studies and 4.3 polytherapy).

8. Safety aspects

Referred to is the ICH E1 guideline.

Identified adverse events should be characterised in relation to the duration of treatment, the dosage, the recovery time, age and other relevant variables. Clinical observations should be supplemented by appropriate laboratory tests and cardiological recordings.

All adverse events occurring during the course of clinical trials should be fully documented with separate analysis of serious adverse drug events, adverse events leading to drop-outs and patients who died while on therapy.

Any information available concerning clinical features and therapeutic measures in accidental overdose or deliberate self poisoning should be provided.

Special efforts should be made to assess potential adverse effects that are characteristic of the class of drugs being investigated depending on the action on various receptor sites. For example if a dopamine agonist of the ergoline group is studied special effort should be made to detect fibrotic adverse events related to these drugs.

8.1. Neurological adverse events

Special attention should be given to the occurrence or exacerbations of neurological adverse events. Also the effect of withdrawal of the test drug should be systematically monitored.

8.2. Psychiatric adverse events

Specific attention should be paid to the occurrence of hallucinations, depression, psychosis and cognitive decline depending on the class and the interactions with various receptor effects. Specific claims in this respect have to be based on specific studies.

8.3. Endocrinological Adverse events

Investigation of neuro-endocrinological variables (e.g. prolactin) is recommended.

8.4. Cardiovascular events

The effect of the medicinal product on the cardiovascular system, occurrence of orthostatic hypotension should be investigated.

8.5. Long-term safety

The total clinical experience must generally include data on a large and representative group of patients (see EC Guideline on population exposure).

For the moment, studies on morbidity and mortality are not required before marketing. However, effects on mortality and morbidity should be monitored on a long-term basis. This can be done post-marketing.

Definitions

The terms used in the guidance concerning Parkinson's disease e.g. de novo Parkinson's, early Parkinson's disease, advanced Parkinson's disease patient are considered working definitions based on clinical practice and not intended to define exact and mutually exclusive patient populations.

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